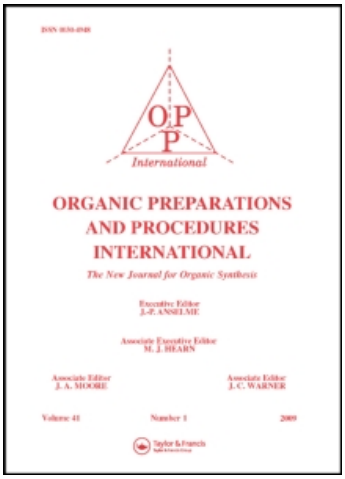

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

DIELS-ALDER REACTIONS OF CYCLOALKENONES IN ORGANIC SYNTHESIS

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To cite this Article Fringuelli, Francesco , Taticchi, Aldo and Wenkert, Ernest(1990) 'DIELS-ALDER REACTIONS OF CYCLOALKENONES IN ORGANIC SYNTHESIS', Organic Preparations and Procedures International, 22: 2, 131 — 165
To link to this Article: DOI: 10.1080/00304949009458194
URL: http://dx.doi.org/10.1080/00304949009458194

ORGANIC PREPARATIONS AND PROCEDURES INT. 22(2), 131-165 (1990)

DIELS-ALDER REACTIONS OF CYCLOALKENONES IN ORGANIC SYNTHESIS. A REVIEW

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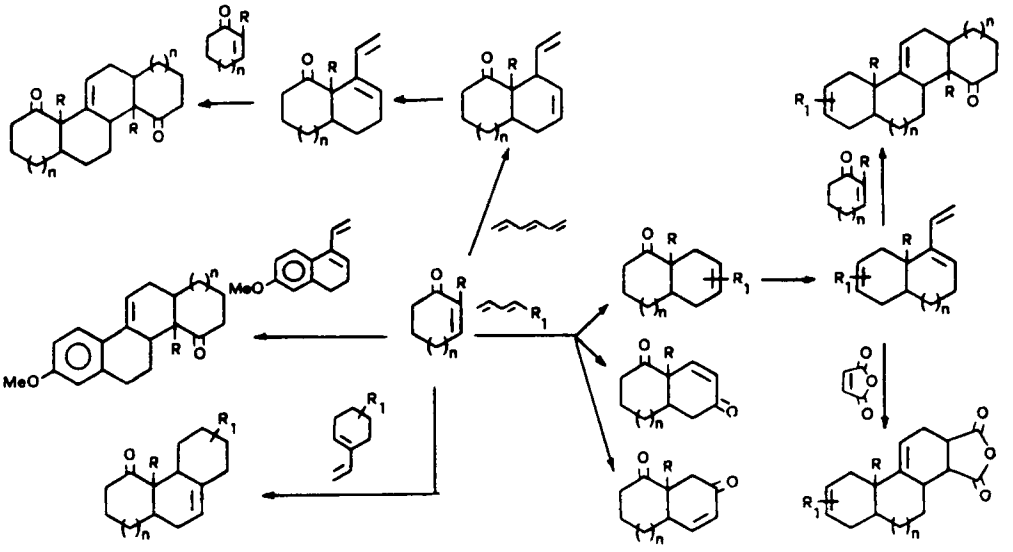
INTRODUCTION

The Diels-Alder reaction of cycloalkenones and 1,3-dienes is, in principle, a simple method of construction of the basic skeleta of sesquiterpenes, diterpenes, steroids and alkaloids. This strategy of synthesis attracted the attention of research workers since 1935, especially because of the high stereospecificity of the reaction and the possibility of building polycyclic systems in two to three steps.[1] A few octalones, hydrindanones and steroid ketones were prepared[2] by the use of α,β-unsaturated cycloalkenones according to the approaches depicted in Scheme 1. The cycloadditions, executed under thermal conditions (175-280°), occurred in low yield and most of the structures of the cycloadducts remained undetermined.

The 1960 discovery[3] of Lewis acid catalysis increasing the reactivity regio- and diastereoselectivity, and yield of the Diels-Alder reaction, should have promoted a reinvestigation of the (4+2)-cycloaddition of 2-cycloalkenones, but new annulation methods (*e.g.*, Robinson annulation) had superceded the Diels-Alder scheme of synthesis. Moreover, the results of the

Scheme 1



first attempts to catalyze the cycloadditions of 2-cyclopentenone, 2-cyclo-hexenone and a few of their alkyl derivatives with alkyl-1,3-butadienes were not encouraging.[4]

However, this research area received new attention in the last decade as a consequence of the discovery of new functionalized dienes and the accurate investigation of the parameters involved in the cycloaddition process. Conjugated cycloalkenones (2-cycloalkenones) were preferred over nonconjugated ones in view of the increased dienophilicity of carbon-carbon double bonds conjugated to a carbonyl group. A rare example of a Diels-Alder reaction of nonconjugated cycloalkenones was that achieved between 4-methyl-3-cyclohexenone and 3-carbomethoxy-2-pyrone (150°, 24 h, 25%) in the course of the total synthesis of the copaenes and ylangenes.[5]

The present review is devoted to the Diels-Alder reaction of 2-cyclo-alkenones.

I. REACTIVITY

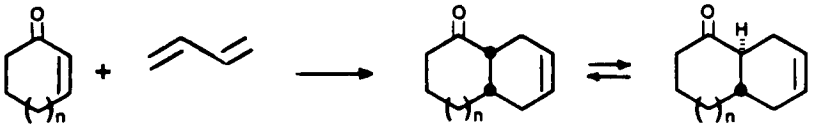
2-Cycloalkenones are dienophiles of low reactivity and their

Diels-Alder reaction usually required drastic thermal reaction conditions.

The reaction usually is kinetically controlled and the adducts seldom give (4+2)-cycloreversion. Retro Diels-Alder reactions have been observed on heating the adducts of trans-2-cyclooctenone with cyclopentadiene and isoprene,[11a] and on treating the formal adduct of 4-methyl-3-carbomethoxy-2-cyclopentenone and cyclopentadiene with $BF_3.Et_2O$ at room temperature.[11b]

The coordination of the carbonyl function with Lewis acids increases the reactivity of dienophile as well as the yield (Scheme 2)[6] and influences the cycloaddition selectivity too (see below). A systematic study[7] of the effect of specific reaction parameters has shown that ketone-catalyst complexation is a key step, influencing dramatically the product yield. The catalysts generally used are $AlCl_3$, $AlBr_3$, $BF_3.Et_2O$, $ZnCl_2$, $SnCl_4$, and $EtAlCl_2$. Lanthanide shifts reagents [$Yb(fod)_3$] have also been employed[8] in the presence of highly reactive or acidsensitive dienes.

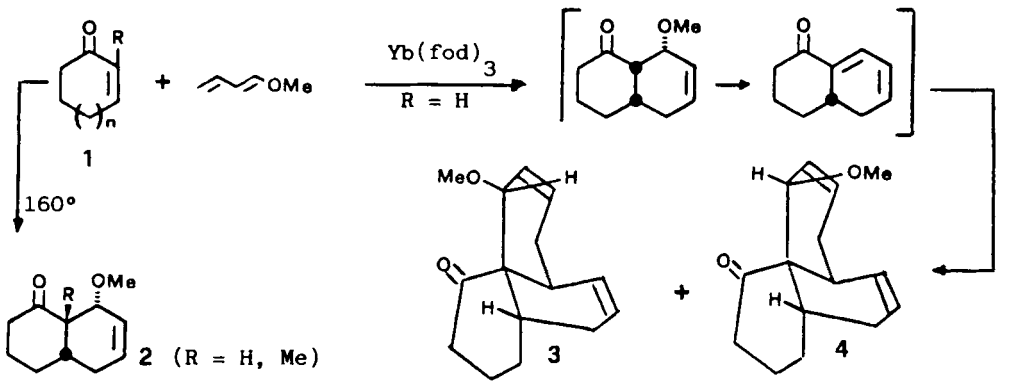
Scheme 2



n	Reaction Conditions	Trans/Cis	Yield (%)
0	110°C 228 h	1:1.5	29
	70°C 5 h $AlCl_3$	1.2:1	95
1	185°C 72 h	9:1	11
	70°C 22 h $AlCl_3$	9:1	84
2	150°C 65 h	1:1.7	15
	25°C 15 h $AlCl_3$	1:12	98

The catalyst can, sometimes, induce epimerization of the primary cis-adducts at their α-keto carbon centers (Scheme 2) and also can cause side reactions, as, for example, in the reaction of 2-cyclohexenone (1, n = 1, R = H) with 1-methoxybutadiene (1→2 and 1→3+4).

The accepted, concerted mechanism of the reaction generally is not



affected by the catalyst.[9] An exception is the $AlCl_3$-catalyzed cyclo-addition of 2-phenyl-2-cyclohexenone with butadiene, wherein a zwitterionic intermediate has been invoked to justify the formation of trans-fused cycloadducts.[4a]

Attempts to induce photochemically the Diels-Alder reaction of cyclic α,β-unsaturated enones are rare, and in cases where this process is observed, mixtures of (2+2) and (4+2) adducts are obtained. Thus 2-cyclohexenone and 2-cyclopentenone and a variety of dienes give principally the expected (2+2) photochemical cycloadducts; (4+2) adducts are observed in low yield only in the reactions with furan or cyclopentadiene.[10] The irradiation of cis-2-cycloheptenone and cis-2-cyclooctenone in the presence of isoprene or cyclopentadiene gives trans-fused Diels-Alder adducts in good yield. The true dienophiles appear to be the trans-enones that are formed in situ by ultraviolet cis-trans isomerization.[11a] Under Lewis acid catalysis, the reaction of cis-2-cyclooctenone and butadiene gives the cis-fused adduct, that is stable under the conditions employed.[12]

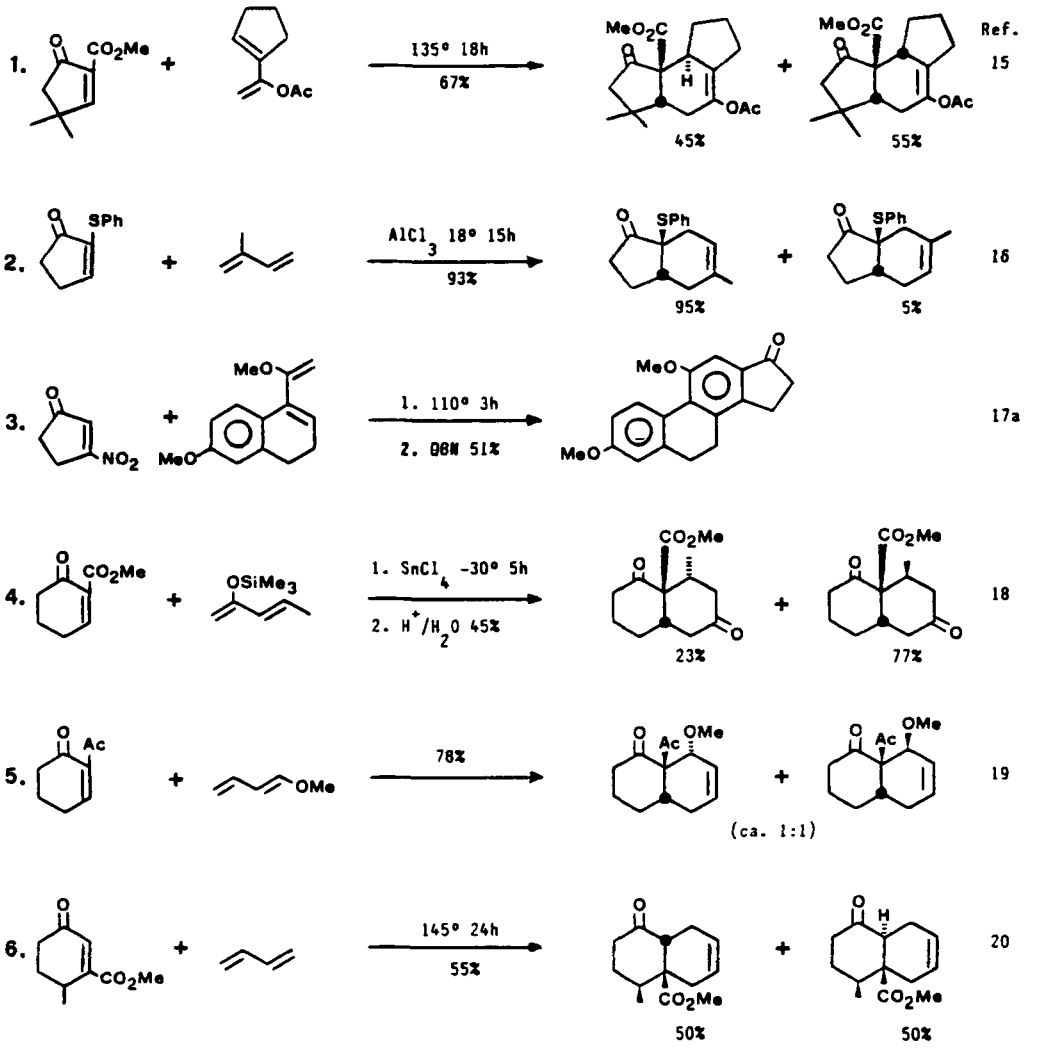
The reactivity of the cycloalkenone system depends on the ring size and the substituents. The reactivity order of unsubstituted ketones in the $AlCl_3$-catalyzed cycloadditions with butadiene is: 2-cycloheptenone>2-cyclo-pentenone>2-cyclohexenone.[6,13] The only report on the Diels-Alder reaction of cyclobutenones concerns the cycloadditions of 4,4-dimethylcyclobutenone with 1,3-diphenylisobenzofuran and cyclopentadiene.[14] The dienophilicity of

the four membered ring in the reaction with cyclopentadiene appears to be superior to that of the six-membered analogue.[14]

Electron-withdrawing groups on the dienophile and electron-donating groups on the diene increase the rate of the cycloadditions, that sometimes occur without catalyst. Examples of these "normal" thermal Diels-Alder reactions are reported in the Scheme 3.

An alkyl group attached to C-2 of the 2-cycloalkenone lowers the

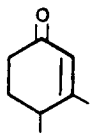
Scheme 3



reactivity of the dienophile, but the reaction succeeds in excellent yield under catalysis conditions.[7] On the contrary, a methyl group at C-3 prevents the intermolecular cycloaddition, both under thermal and under catalysis conditions. Compounds 5[15], 6[7,21], 7[20b] and 8[22] are examples of unreactive dienophiles. Intramolecular cycloadditions of compounds whose 2-cycloalkenone part is alkylated at C-3 generally occur (see below).

5

6 R = Me
= Morpholino
= Pyrrolidino



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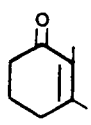
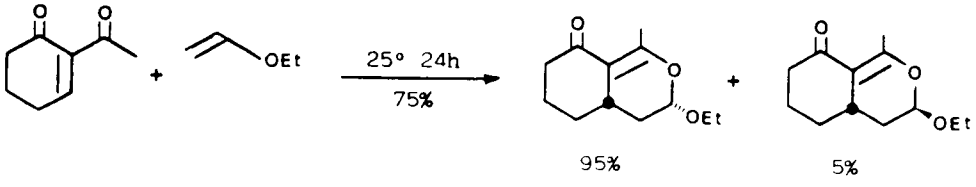
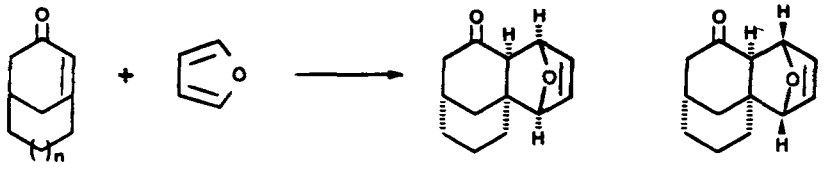


8

The presence of a 2-keto group on the enone system causes Diels-Alder reactions of "inverse electron demand", with enol ethers and enamines, as for example, in the cycloaddition of 2-acetyl-2-cyclohexenone (1, n = 1, R = COMe) with vinyl ethyl ether.[19] These adducts are useful for the synthesis of secoiridoids and their analogs:



Distortion of the conjugated enone system from planarity increases the reactivity of the dienophile, and relief of the angle strain of the carbon-carbon double bond during cycloaddition, provides substantial driving force for the above mentioned reactions of 4,4-dimethylcyclobutenone, trans-2-cycloheptenone and trans-2-cyclooctenone. Other significant examples are the reactions of the bridgehead enones 9 studied by House and



9 (n = 1,2,3) **10** (72%) **11** (28%)

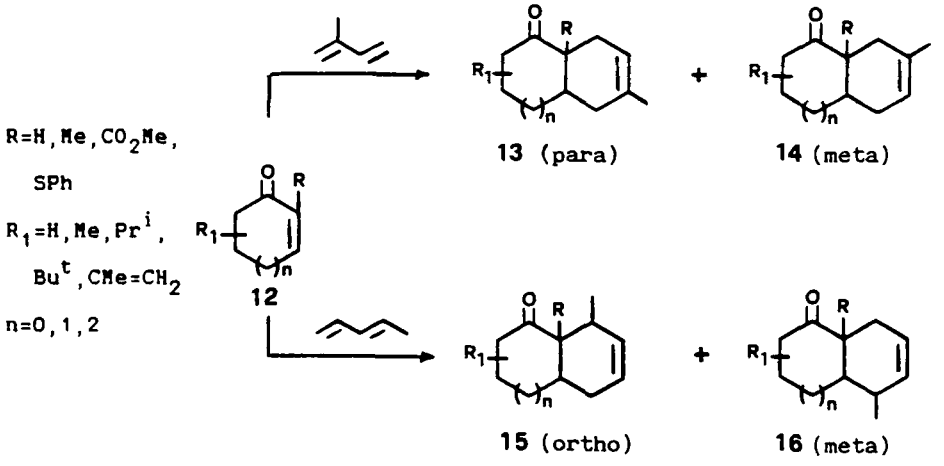
coworkers.[23] The double bond of the bicycloalkenones 9 becomes less twisted as the number of methylene groups increases.[23b] As consequence only 9 (n = 1) forms cycloadducts with furan (23°, 12 h, 86%) with a prevalence of the exo-adduct 10.[23c,d] 2-Cyclohexenone on the contrary fails to react with 2-methylfuran.[24]

II. SELECTIVITY

a. Regioselectivity

The regiochemical outcome of the Diels-Alder reaction of 2-cyclo--alkenones with unsymmetrical dienes depends on the electronic nature of the substituents and their ring position. The selectivity of the cycloaddition is influenced dramatically by Lewis acids.[6,16,25]

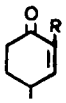
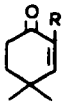
2-Substituted and 2,3-unsubstituted cycloalkenones 12 show high



regioselectivity in the Lewis acid catalyzed cycloadditions with isoprene and E-piperylene in favour of adduct types 13 and 15, respectively, in agreement with the "para-ortho" rule.[16,18,25,28-31] The same behavior is observed in the cycloadditions with other 1- and 2-substituted butadienes bearing 1-OMe,[8,19] 1-$NHCO_2Et$,[32] 1-$(CH_2)_4NO_2$,[33] 2-OEt,[24,34] 2-CH_2SiMe_3,[35] 2-$OSiMe_3$[36] and 2-$OPOAr_2$ substituens.[37] The "para-ortho" rule is observed similarly in the reactions with di- and poly-substituted butadienes. Some examples are shown in Scheme 3.

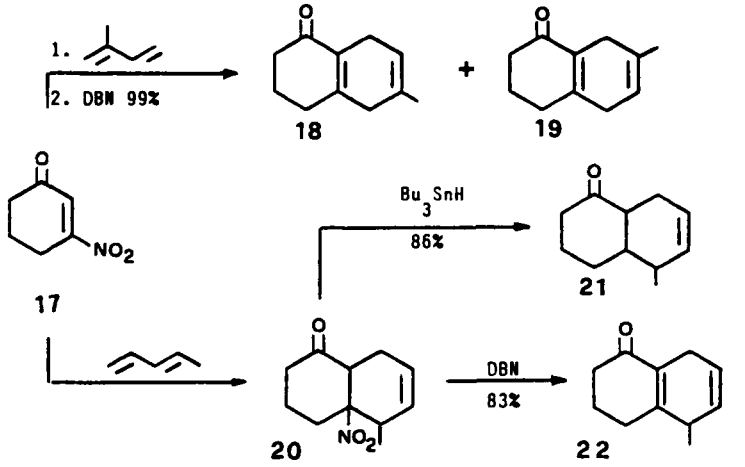
Exceptions are the 4,4-dimethyl-2-cyclohexenone and its 2-methyl derivative, which with isoprene give equal amounts of adduct types 13 and 14 even in the presence of catalyst[27] (Table 1). A complete "para" selectivity is also observed[29] when the C-2 substituent is a carbomethoxy

Table 1. Percentage of Para Adducts in the Lewis Acid Catalyzed Cycloadditions of Cyclohexenones and Cyclohexadienones with Isoprene[a]

Dienophile	R = H	Me	CO_2Me
	100 (6)	100 (6)	100 (18)
	100 (28)	97 (25)	
	50 (6)	58 (27)	100 (29)
	0 (26)	0 (26)	30-82 (26)

a) References in parentheses

group (Table 1). The Lewis acid-catalyzed cycloadditions of the 4,4-di--methylated compounds with E-piperylene always are completely "ortho"-selective.[25,29] 5,5- and 6,6-dimethylcyclohexenones as well as 2,6,6-tri--methylcycloheptenone show a high regioselectivity in the cycloaddition with isoprene and E-piperylene in the presence of $AlCl_3$ in favour of "para" and "ortho" adducts.[6,25] The C-4 gem-dimethyl effect has been explained in terms of steric effects and secondary orbital interactions in the exo and endo transition states.[25,29] These results are of theoretical and synthetic



interest expecially when compared with those of analogous 4,4-dimethyl--cyclohexadienones[26] (Table 1).

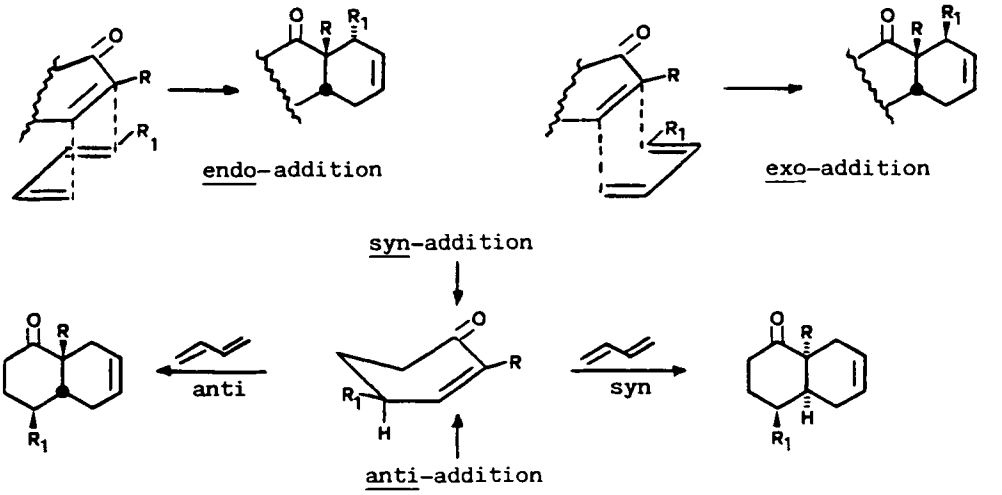
A high or total preference for adduct types 14 and 16 is observed when strong electron-withdrawing substituents, such as the NO_2 group, are attached to C-3 of the cyclohexenone ring[17a] (17→18+19; 17→20). Treatment of the adducts with diazabicyclo(4.3.0)non-5-ene (DNB)[17a] or with Bu_3SnH[17b] effects rapid conversion of the β-nitrocarbonyl system into an α,β-enone (20→22) or saturated keto unit (20→21), respectively.

b. Diastereoselectivity

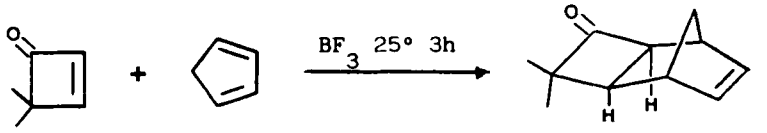
The diastereoisomerism of the Diels-Alder reaction is determined by two spatial orientations of the reactants known as endo-exo and syn-anti addition modes (Scheme 4).

2-Cycloalkenones give usually endo-addition.[28,30,41] When, however a methyl group or an oxygenated function, such as a carbomethoxy group are attached to C-2 or a gem-dimethyl group is present in the ring, exo-addition is either predominant or exclusive.[18a,38,39,40] as for example, in

Scheme 4



the high exo-diastereoselectivity of the reaction of 4,4-dimethyl--cyclobutenone (23) with cyclopentadiene[14] and the cycloadditions of some 2-cyclohexenones with E-piperylene and cyclopentadiene (Tables 2 and 3).



23

Similarly, the reaction of 2-carbomethoxy-4,4-dimethylcyclopentenone with 1-(α-acetoxy-vinyl)-cyclopent-1-ene (Scheme 3, entry 1) gives a 45:55 mixture of exo and endo adducts under thermal conditions and a high exo-diastereoselectivity (97%) in the presence of a Lewis acid catalyst ($AlCl_3$, -78°->25°, 6 h, 62%).[15]

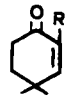
These deviations from endo preference have been explained by invoking steric interactions, electronic effects, and secondary orbital interactions.[18a,38-40] The problem is complicated by the interplay of many factors including the size of the ring and the type of diene. Thus, the 2-methylcyclopentenone (1,n = 0, R = Me) reacts[42] with vinylcyclohexenes 24

Table 2. Percentage of Endo-Addition of the Catalyzed Diels-Alder Reactions of 2-Substituted 2-Cyclohexenones with E-Piperylene and Cyclopentadiene

Substituent	E-Piperylene	Cyclopentadiene
H	97[a]	89[b]
Me	70[a]	30[b]
Pr^i	94[a]	
CO_2Me	44[c]	0[c]

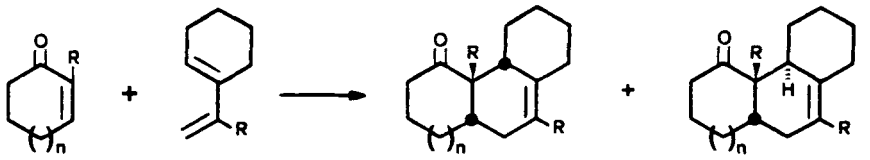
a) $AlCl_3$, Ref.38 b) $AlCl_3$, Ref.40 c) $SnCl_4$, Ref.18a

Table 3. Percentage of Endo-Addition of the Catalyzed Diels-Alder Reactions of Geminaldimethylated-2-Cyclohexenones with E-Piperylene and Cyclopentadiene[a]

Dienophile		E-Piperylene	Cyclopentadiene
	R=H	97	95
	R=Me	97	60
	R=H	99	79
	R=Me	97	29
	R=H	78	42

a) $AlCl_3$, Ref.38,40

(R = H, $OSiMe_2Bu^t$) to give endo adducts 25 (R = H, $OSiMe_2Bu^t$), whereas the cycloaddition of 2-methylcyclohexenone (1, n = 1, R = Me) with 1-(α-tri-

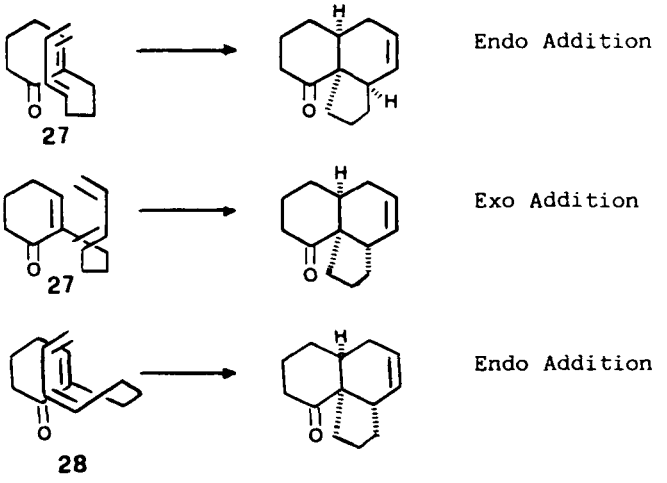


1 24 25 (endo) 26 (exo)

methylsilyloxyvinyl)cyclohex-1-ene (24, R = $OSiMe_3$) gave only exo adduct 26 (R = $OSiMe_3$).[43] Again, 2-methylcyclopentenone and 2,6,6-trimethyl--cycloheptenone afforded only endo adducts in the $AlCl_3$-catalyzed Diels--Alder reaction with E-piperylene,[6] whereas 2-methylcyclohexenone gave 70% of endo addition.[38]

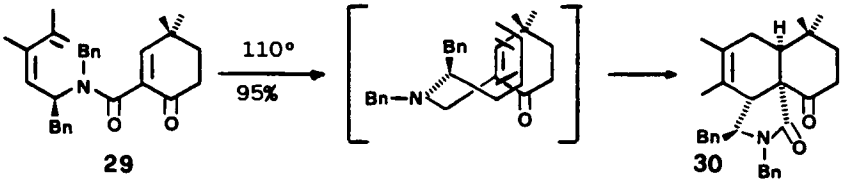
The endo-exo diastereoselectivity in intramolecular Diels-Alder reactions depends on the configuration of diene and the length of the chain between diene and dienophile. Compounds such as 27 (Scheme 5), possessing

Scheme 5



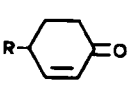
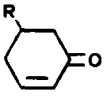
an E-diene unit, give endo and exo addition, but for a diene with Z configuration (e.g., 28) only endo addition is possible. The conversion of chiral Z-amide 29 into lactam 30, executed in model studies directed to the synthesis of cytochalasin C, serves as illustration of this strategy.[44]

The syn-anti diastereoselectivity (π-facial stereoselectivity) has been studied in detail in the catalyzed cycloaddition of a variety of alkyl-substituted 2-cyclohexenones with butadiene, isoprene and E-piperylene.[28,30,45] The results (some of them illustrated in Table 4)



have revealed that the preferential syn- or anti- addition to flexible dienophiles cannot be predicted merely on the basis of consideration of

Table 4. Percentage of Anti-Diastereoselectivity in the Catalyzed Diels-Alder Reactions of 4- and 5-Substituted 2-Cyclohexenones[a]

Diene	R=	 Me	Pr^i	Bu^t	 Me	Pr^i	Bu^t
		55	67	100	96[b]	92	97
		90	91	100	97	92	91
		49	61	100	96	98	97

a) $AlCl_3$, Ref.28,30,45 b) BF_3, 100%, Ref. 46

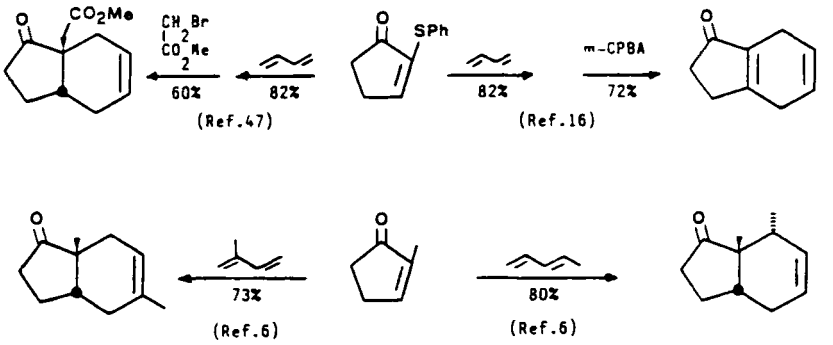
steric factors (i.e., by determining the more sterically hindered face), but also involves consideration of the conformational equilibrium, the conformational reactivity of the dienophile, and the stereoelectronic control of the transition state.[45]

III. SYNTHESIS

a. Bicycloalkenones

Bicyclic systems such as hydrindanones, octalones and hydrobenzosuberones are used frequently as starting materials for synthesis of natural products. Construction of some intermediates by Diels-Alder reactions of simple 2-cycloalkenones with a variety of dienes and subsequent elaboration of the adducts are illustrated in Schemes 6-8.

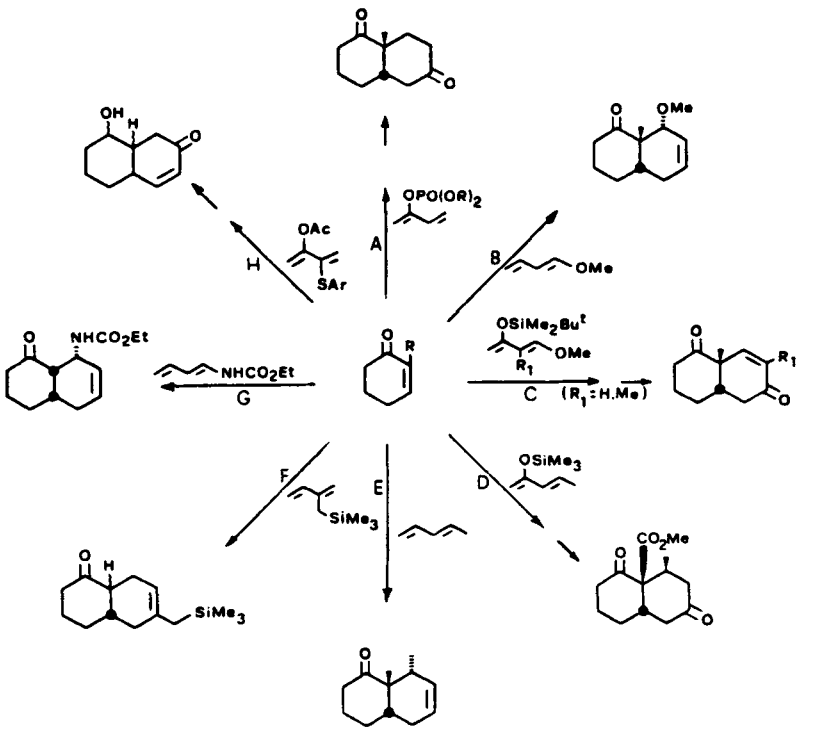
Scheme 6



For example, the transformation of hydrobenzosuberone 31, (Scheme 9) available in large quantity[50], into dienone 32 provides a key compound in the synthesis of diacid 33, which represents the "7-epi-bottom half" of the antibiotic aglycon of chlorothricolide.[51]

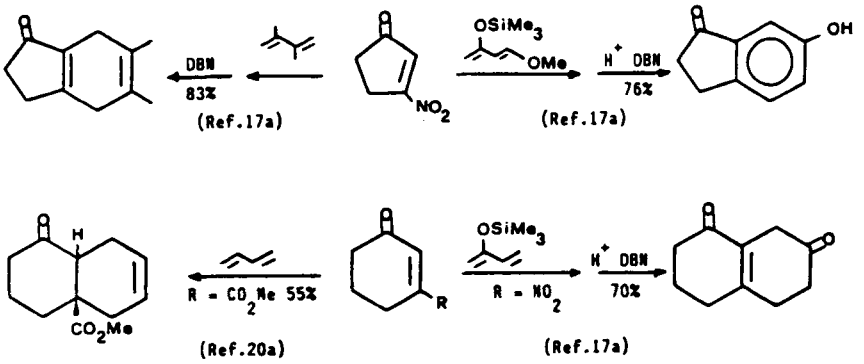
The lack of reactivity of 3-methyl-2-cycloalkenones both in thermal and catalyzed intermolecular Diels-Alder reactions precludes the

Scheme 7

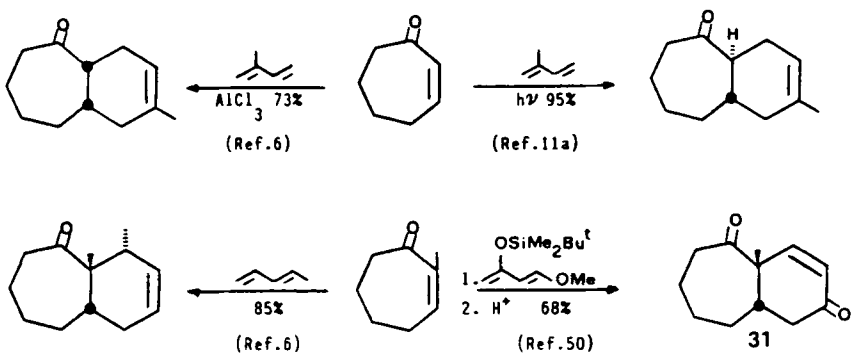


A[37], 30%; B[8], 32%; C[48], 42%; D[18a], 45%; E[6], 92%; F[35], 70%; G[32], 88%; H[49], 85%.

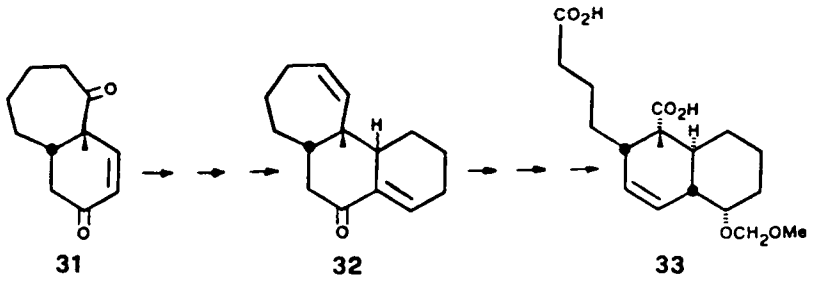
Scheme 8



Scheme 9

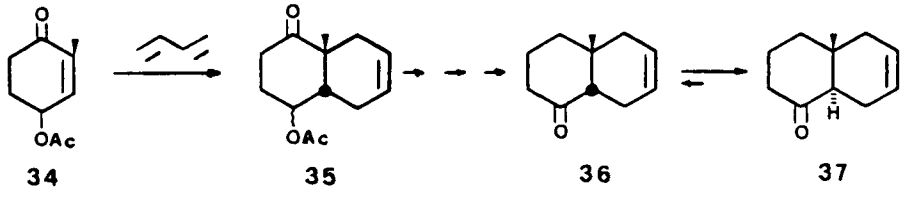


preparation of bicycloalkenones with the angular methyl group in 1,3-positional relationship with the keto function. A 4-acetoxy group on the dienophile allows a resolution of the problem.[52] Thus, enone 34 undergoes

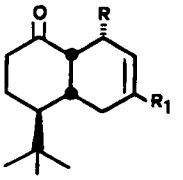


reaction with butadiene [52] to give a mixture of adducts 35. The latter can be converted into the cis-octalone 36 in good yield. Base-induced isomerization of the product gives trans ketone 37.

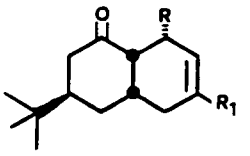
The t-butylated bicyclic adducts 38 and 39, easily prepared by



catalyzed Diels-Alder reaction of 4- and 5-t-butyl-2-cyclohexenone and butadiene, isoprene and E-piperylene, were important in the area of conformational analysis.[28,30]



38 R, R_1 = H, Me



39 R, R_1 = H, Me

b. Sesquiterpenes

In recent years, numerous key compounds in the synthesis of natural sesquiterpenes have been prepared by Diels-Alder reactions of 2-cycloalkenones. A survey is reported in Table 5 and some cycloadditions are discussed briefly.

All three chiral centers in the cadinene skeleton (Table 5, entries 1 and 2) are constructed by taking advantage of the high anti-para selectivity of the Diels-Alder reaction of 4-alkylated 2-cyclohexenones, with isoprene[30], and the acid epimerization at the ring junction of the initial cis-fused adduct. Asymmetric syntheses are achieved by using (-)-cryptone (41) as dienophile.

The ketoesters 43 are good starting materials to prepare 4a-methyl--1-octalones such as 37 and 50 that, as observed previously, are not accessible by direct Diels-Alder reaction of 3-methyl-2-cyclohexenones. The face-selectivity of the cycloaddition of 43 (R = Me) with butadiene (Table 5, entry 4) depends markedly on the presence of the catalyst. Torii, et al.[55] found only 51 and 52 (100% anti-addition) in the thermal (160°) cycloaddition and converted 52 into 50, which was subsequently used to synthetize the (±)-dehydrofukinone. Piers and Hall [20b] reported that equal amount of 52 and 53 (anti/syn = 1) are obtained, when the reaction is catalyzed by $AlCl_3$, in agreement with the behaviour of 4-methyl- and 4-acetoxy-2-cyclohexenone.[30,52] The last authors found the 52->50

Table 5. Synthesis of Sesquiterpenes by Diels-Alder Reactions of 2-Cycloalkenones

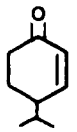
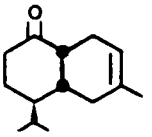
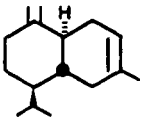
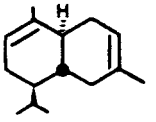
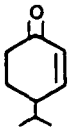
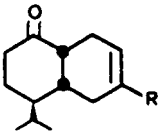
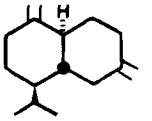
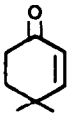
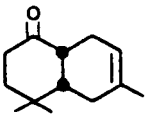
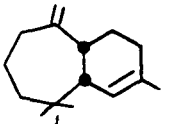
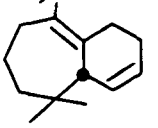
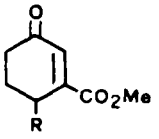
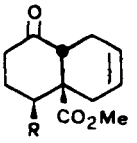
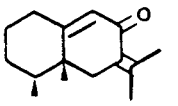
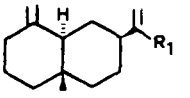
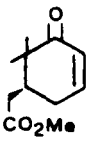
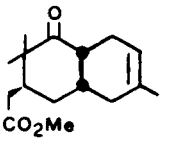
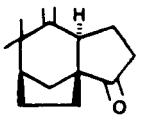
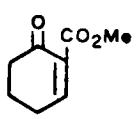
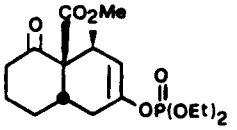
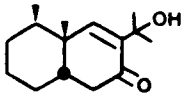
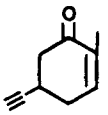
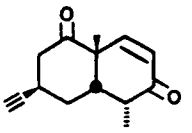
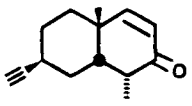
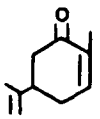
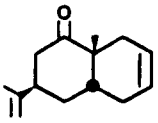
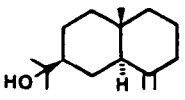
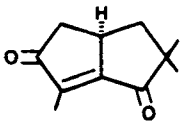
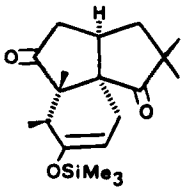
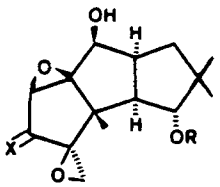
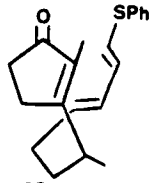
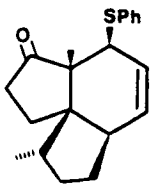
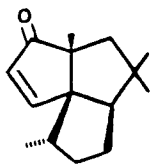
	Ketone	Adduct	Sesquiterpene	Ref.
1.	 **40**		 (±)γ_2-Cadinene	35,53
			 (±)β-Cadinene	53
2.	 **(-) 41**	 R: OEt, CH_2SiMe_3	 (+) ε-Cadinene	34,35 54
3.	 **42**		 (±)α-Himachalene	27
			 (±)β-Himachalene	27
4.	 **43** R: H, Me		 (±)Dehydrofukinone	55
			 R_1 = CH_2OH β-Costol	56
			R_1 = CHO α-Costal	56
5.	 **(-) 44**		 (-)Khusimone	57

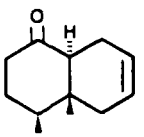
Table 5. (continued)

	Ketone	Adduct	Sesquiterpene		Ref.
6.	 **45**			(±)Petasitolone	58
7.	 **46**			(±)Chamaecynone	59
8.	 **(-)47**			(-)β-Eudesmol	31,60
9.	 **48**			(±)Coriolin X = O, R = H (±)Coriolin B X = β-OH, α-H R = $CO(CH_2)_6Me$	61
10.	 **49**			(±)Oxosilphinene	62

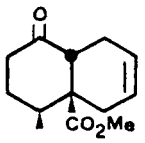
conversion unattractive and prepared the octalone by an alternate route.

The cycloaddition of 44 with isoprene[57] (Table 5, entry 5) also illustrates the influence of experimental conditions on the diastereofacial selectivity. Contrary to the high anti-selectivity of 5-alkyl-2-cyclohexenones, the ketoester 44 gives a syn-anti selectivity strongly

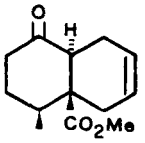
dependent on the type and equivalents of catalyst, the reaction time, and the complexation time. With 0.1 equivalents of $SnCl_4$, 4.5 hrs. of



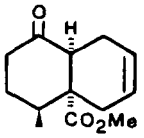
50



51



52

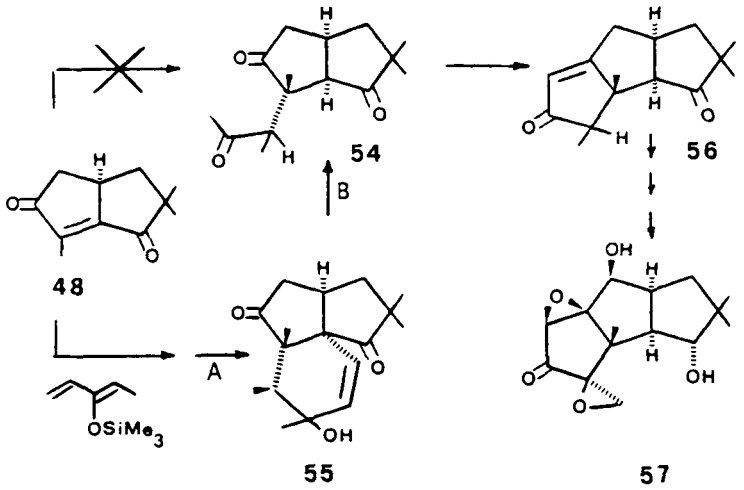


53

complexation time, 11 equivalents of isoprene and a reaction time of 48 hrs. at room temperature, only anti addition was observed and the adduct (**Table 5**, entry 5) was subsequently converted to (-)-khusimone.

The optically active carvone (**47**), a naturally occurring 5-alkylated 2-cyclohexenone, gives selectively anti-cycloadditions and allows the construction[31,60] of the 1,4-methyl-isopropyl cis-relationship in the eudesmane series (**Table 5**, entry 8).

The Diels-Alder reaction coupled with the opening of the six-membered ring can be used in lieu of the Michael reaction. An example of this cycloaddition-degradation sequence exists in the synthesis of (±)-coriolin[61] (**Table 5**, entry 9). The direct Michael reaction of **48** fails to yield the



A : PhSeCl; H_2O_2; LiMe B : O_3; CrO_3; $Ba(OH)_2$; $Pb(OAc)_4$

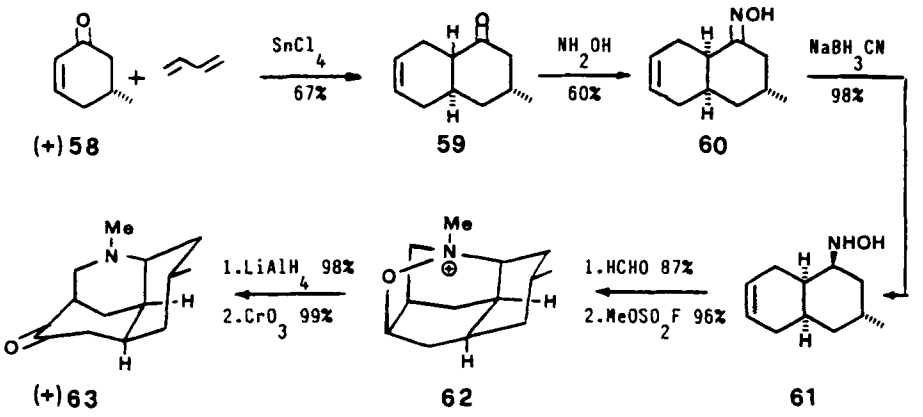
key intermediate 54 because the reaction leads to the introduction of an acetonyl group to the junction carbon. The synthesis of 54 was achieved by Diels-Alder reaction of 48 with E-1-methyl-2-trimethylsilyloxybutadiene and degradation of the allylic alcohol 55. The syn-addition of the diene relative to the junction hydrogen of 48 is expected, since the anti addition would result in an energetically prohibitive trans fusion of the two five-membered rings. The regioselectivity of the cycloaddition is determined both by the directing effect of the diene methyl group, which usually predominates over the 2-heterosubstituent and by the α-methyl--cyclopenthenonic system. Aldolization-dehydration of 54 affords 56, which then is converted in a few steps into (±)-coriolin (57) and (±)-coriolin B (Table 5, entry 9).

The key step in the synthesis of the angular tricyclopentenoid sesquiterpene (±)-3-oxosilphinene[62] (Table 5, entry 10) is the intramolecular Diels-Alder reaction of sulphenyltriene 49. It is interesting to observe that 49 is an example of a reactive 3-alkylated 2-cycloalkenone. The cycloaddition occurs through an exo-transition state, and the adduct has all four contiguous chiral centers with the required stereochemistry. The cycloadduct is then converted into the natural product via contraction of the six-membered ring.

c. Alkaloids

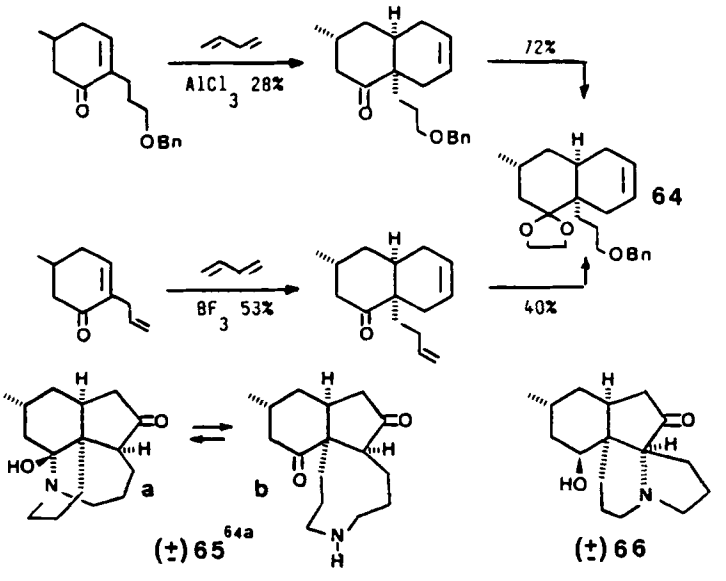
The anti-diastereoselectivity of the Diels-Alder reaction of 5-alkyl-2-cyclohexenones with butadiene and its alkyl derivatives (Table 4) has been used profitably for the preparation of key intermediates in the synthesis of alkaloids such as (+)-luciduline,[63] (±)-fawcettimine,[64] (±)-8-deoxy-serratinine,[64] and (±)-dendrobine.[65]

The two fused six-membered carbocyclic rings and the required configuration of three chiral centers of the natural alkaloid, (+)-luciduline (63), were achieved[63] by the catalyzed Diels-Alder reaction of (+)-5-methyl-2-cyclohexenone (58) and butadiene. Lewis acid promoted epimerization of the cis adduct, which was removed from the equilibrium



mixture 59 by selective transformation into the oxime 60. The heterocyclic ring was constructed by a selective intramolecular N-alkenylnitrone addition (61→62).

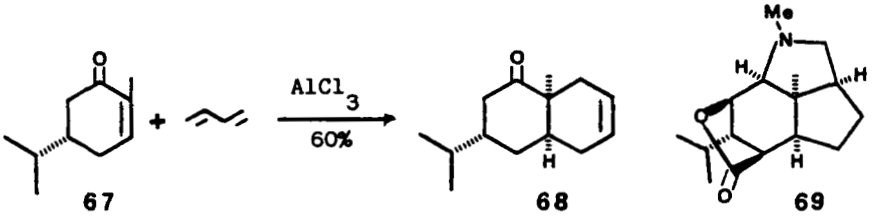
Scheme 10



The key intermediate 64 in the syntheses of the Lypocodium alkaloids, (±)-fawcettimine (65) and (±)-8-deoxyserratinine (66), was prepared stereoselectively[64a] by the two routes illustrated in the Scheme 10. A multi-step

sequence converts 64 into 65 and 66.

The molecular skeleton of dendrobine (69) was constructed[65] by a six-step synthesis from octalone 68, that was obtained by a catalyzed cycloaddition of carvotanacetone (67) and butadiene.

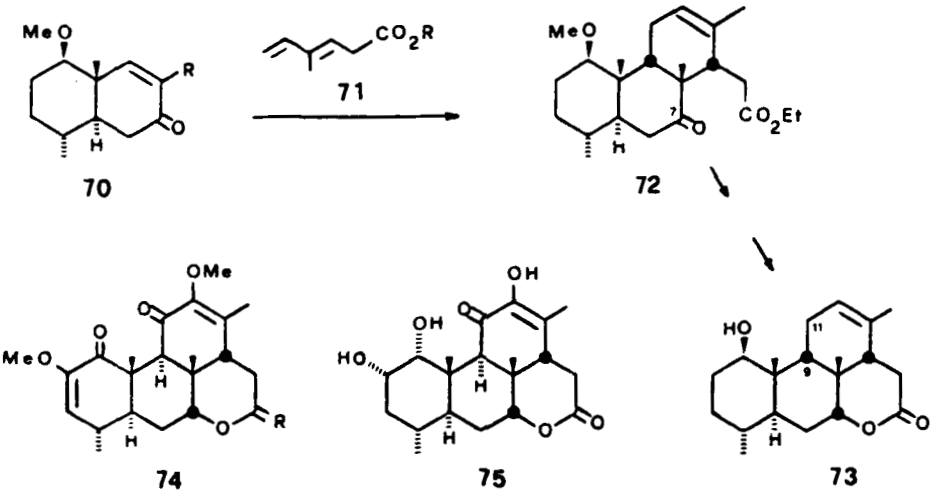


67 68 69

d. Quassinoids

Quassinoids are highly oxygenated naturally occurring triterpenes, whose potent antileukemic activity has stimulated recently biogenetic and synthetic interest. These compounds have complex stereostructures, and the Diels-Alder reactions of 2-cycloalkenones with suitable dienes, offer elegant, short synthetic approaches.

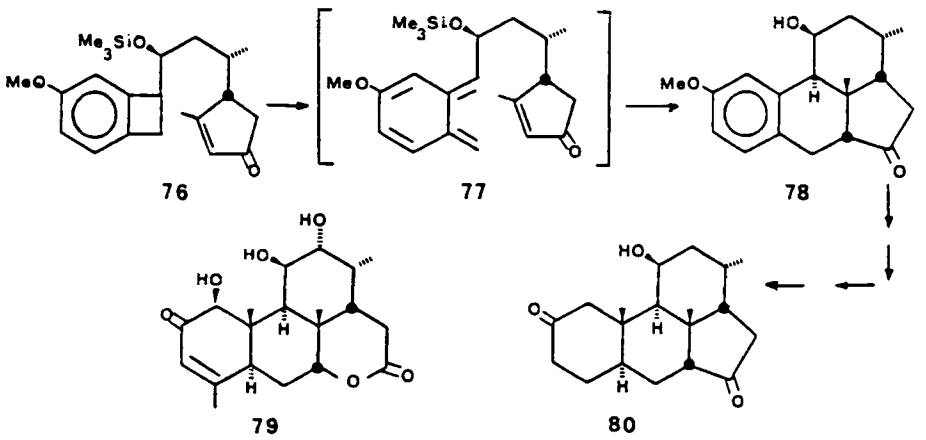
The key intermediate in the synthesis of (±)-quassin (74, R = O)



70 72 74 75 73

(±)-neoquassin (74, R =β-OH,H) and (±)-castelanolide (75) is the tetracyclic compound 73, whose chiral centers (with the exception of C-9) have the required configuration.[66,67] Lactone 73 is the result of anti-endo--ortho-selective cycloaddition ($AlCl_3$, 30 h, PhH, 40%) of octalone 70 (R = Me) and diene 71 (R = Et) and of the stereoselective reduction of the 7-keto group of 72, followed by a lactonization reaction. The required configuration of C-9 was achieved after the 11-keto group was introduced. Quassin (74, R = O) and neoquassin (74, R =β-OH,H) were obtained from 70 (R = Me) with an overall yield of ca. 3-4%.In aqueous medium, the rate of the Diels-Alder reaction of formyloctalone 70 (R = CHO) and diene carboxylic acid 71 (R = H) or carboxylate 71 (R = Na) is strongly enhanced and significant exo-addition is observed.[68]

An alternate stereoselective method for the construction of the quassinoid ring system is the intramolecular Diels-Alder reaction of a o-quinodimethide 77, formed by a conrotatory ring-opening of the benzo-



76 77 78

79 80

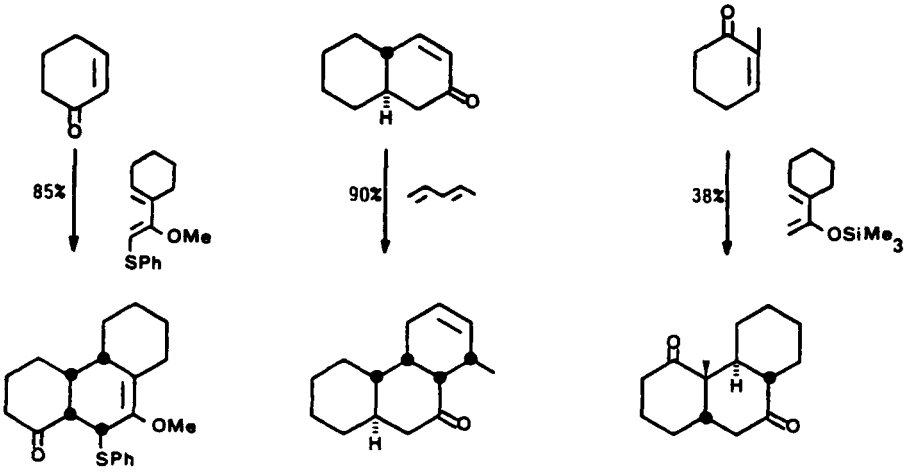
cyclobutane system 76.[69] The cycloaddition occurs through the exo-addition. The tetracyclic ketone 78 was converted into the quassinoid intermediate 80, the chiral centers of which have the same stereochemistry as those of klaineanone (79). The behaviour of 77 shows again the different reactivity

of 3-alkyl-2-cycloalkenones in inter- and intra-molecular Diels-Alder reactions (compare 5-8, 49 and 77).

e. Polycyclic Precursors

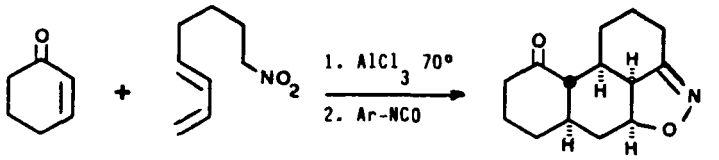
The hydrophenanthrene system is present in naturally occurring compounds, such as diterpenes and steroids, and functionalized hydrophenanthrones are suitable synthetic precursors. The preparation of

Scheme 11



(endo-addition)[70] (endo-anti-addition)[71] (exo-addition)[43]

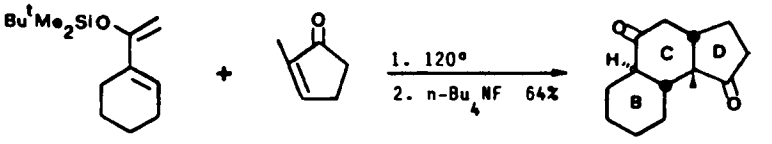
some of them by (4+2)-cycloaddition reactions of 2-cycloalkenones is illustrated in Scheme 11. The versatility of this approach is shown by the fact that the proper choice of diene and dienophile will lead to



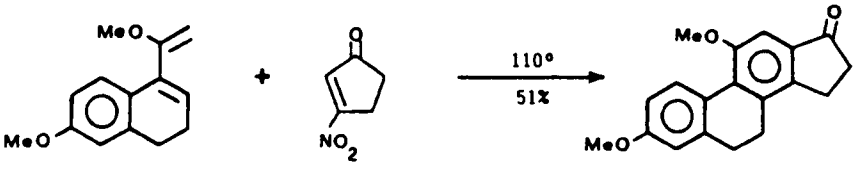
1 (n = 1, R = H) **81**

functionalized intermediates displaying stereochemical variation.[43,70,71]

A hydrophenanthrene system coupled with an isoxazoline ring is prepared



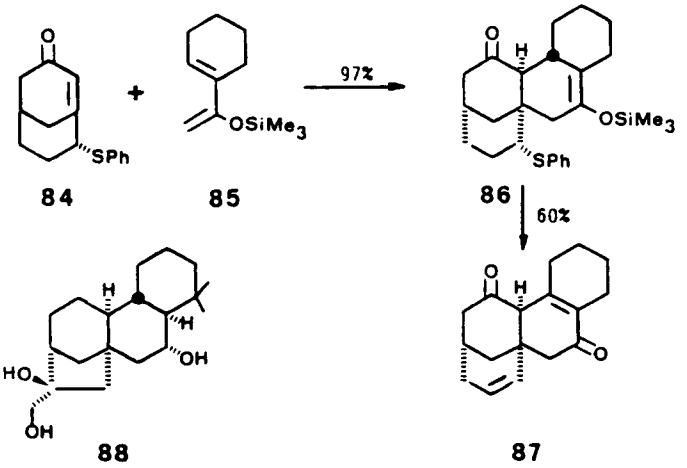
82 (endo-para-addition)



83 (meta-addition)

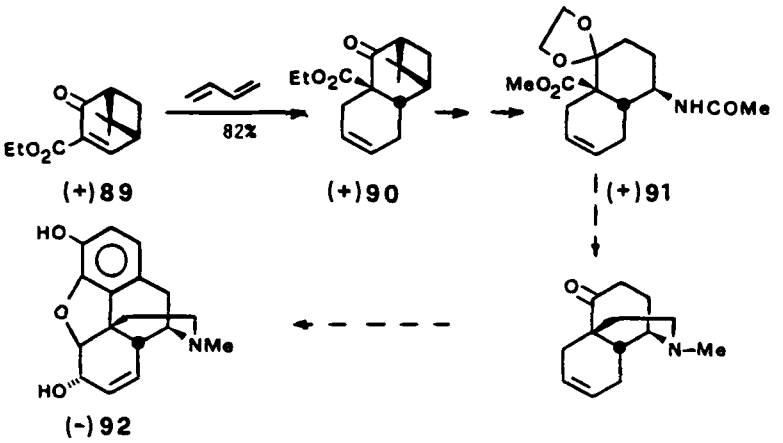
by a (4+2)+(3+2) triannelation process [1, (n = 1, R = H)→81].[33] The heterocyclic ring is a versatile functional array, making this tetracyclic system a possible precursor for quassinoids, steroids, and diterpenoids.

The BCD ring sequence (e.g., 82) or the complete skeleton of a steroidal compound (e.g., 83) is built by the use 2-cyclopentenones and vinylcyclohexenes.[15,17a,42] Endo-addition is preferred, contrary to the observation for 2-methyl-2-cyclohexenone (Scheme 11) and the regioselectivity is controlled by the substituent on the dienophile.



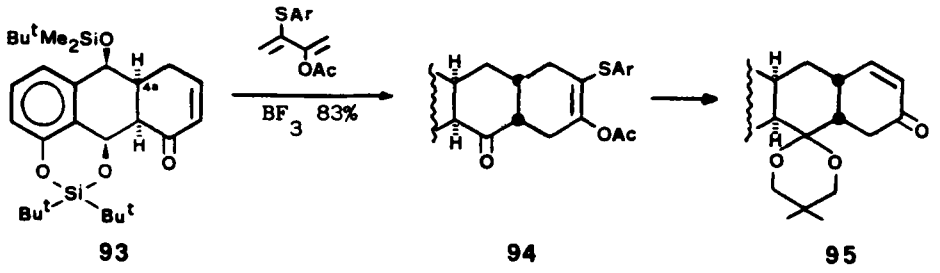
84 **85** **86** **88** **87**

Compounds with the bridgehead double bond are frequently in the field of diterpenes and alkaloids and the Diels-Alder reaction of 2-cyclo--alkenones can be applied profitably for preparation of key precursors. Ketone 86, prepared by syn (to the methane bridge)-exo addition of enone 84 with vinylcyclohexene 85, is converted easily to dienedione 87. The latter ketone has the required stereochemistry and the appropriate functionality to be converted into corymbol 88.[72] Another example is the anti (to the cyclobutane) addition of (+)-ketoester 89 to butadiene. Adduct 90 allows

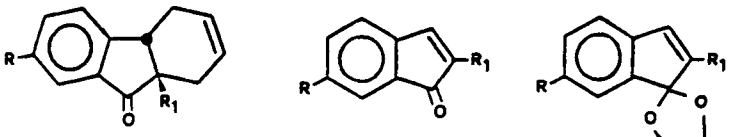


the preparation of the ethyleneketal 91, which is an attractive intermediate for a stereo- and enantioselective synthesis of (-)-morphine (92).[73]

Diels-Alder reactions of 2-cycloalkenones have been also used to prepare linear, fused ring systems (e.g., hydronaphthacenes and hydro-



fluorenes). In a general approach directed to the synthesis of the anthracyclinoid, pillaromicinone, the key intermediate 95 was prepared by taking advantage of the syn (to H-4a)-stereoselectivity of the (4+2)--cycloaddition reaction (93->94) and the directing effect of the sulfide group of the diene.[74]

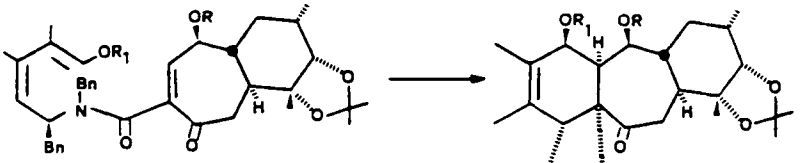


96 97 98

R = H, OMe R_1 = H, CO_2Me

Hydroflurenones 96 are gibberellin precursors and have been prepared[75] by Diels-Alder reactions of the indenone ketals 98 with butadiene and acid-catalyzed deprotection of the carbonyl group or by cycloaddition of indenones 97 generated in situ by acid treatment of 98.

Synthetic applications involving intramolecular Diels-Alder reactions of 2-cycloalkenones are infrequent. An example is the cyclization of ZE-diene 99, which proceeds with endo-stereospecificity (cf. 29->30) to afford 100, a cytochalasin C precursor.[76]



99 (R = $CH_2CH_2SiMe_3$, R_1 = COPh) 100

Acknowledgment.- F.F. and A.T. thank the Consiglio Nazionale delle Ricerche (C.N.R. Roma) and Ministero della Pubblica Istruzione (M.P.I. Roma) for financial support.

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(Received July 17, 1989; in revised form October 25,1989)